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WRITTEN OPINION
(PCT Rule 66)

		Date of mailing (day/month/year)	17.09.2004
Applicant's or agent's file reference A31696M		REPLY DUE	within 3 month(s) from the above date of mailing
International application No. PCT/JP 03/15968	International filing date (day/month/year) 12.12.2003	Priority date (day/month/year) 16.12.2002	
International Patent Classification (IPC) or both national classification and IPC C07D401/14			
Applicant MITSUBISHI PHARMA CORPORATION			

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

When?	See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).
How?	By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.
Also:	For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.
- If no reply is filed**, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 16.04.2005

Name and mailing address of the international preliminary examining authority:	Authorized Officer Von Daacke, A	
 European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Formalities officer (incl. extension of time limits) Siefert, A Telephone No. +49 89 2399-2469	

I. Basis of the opinion

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

Description, Pages

1-46 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
 - ☐ the claims, Nos.:
 - ☐ the drawings, sheets:
5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).
6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

WRITTEN OPINIONInternational application No. **PCT/JP 03/15968**

Novelty (N)	Claims	
Inventive step (IS)	Claims	1-10
Industrial applicability (IA)	Claims	

2. Citations and explanations**see separate sheet**

V REASONED STATEMENT

1. PRIOR ART

The documents cited in the International Search Report

D1: WO00/18758

D2: WO01/70728

D3: WO01/70729

have been considered for the examination procedure.

2. NOVELTY

The claimed subject-matter is considered to be novel (Article 33(2) PCT). The essential structural difference between the claimed compounds and those of D1 relates in the presence of the dihydropyridine substituent in position 2.

3. INVENTIVE STEP

The claimed subject-matter does not fulfil the requirements of Article 33(3) PCT for the following reasons.

The closest state of the art for the present application is represented by D1. D1 discloses structurally similar compounds which may be used in the treatment of diseases caused by abnormal activity of TPK1. In the present application, the structural variation of the D1 compounds, namely the choice of a specific 2-substituent and the alkylation at the pyrimidine nitrogen atom (position 3) is alleged to lead to derivatives with the same qualitative activity as those described in D1. In view of the experimental part and the other information as given in the description, it can be assumed that this problem has been solved for the compounds according to Claim 1.

The problem underlying the present application can, however, not be seen in the provision of further novel pyrimidin-4-one derivatives, because the proposed solution would be seen as obvious.

D1 teaches that R¹ (position 2) may be a heterocyclic substituent. In the description on page 13, a list of various different moieties is disclosed, including different aromatic, partially saturated and saturated heterocyclic systems. Inter alia, pyridine and piperidine are mentioned, but not dihydropyridine. D2 discloses

similar compounds. The 2-substituent may be dihydropyridine which is condensed. A man skilled in the art, aware of the disclosure of D1 and D2, would have obviously expected the same qualitative properties shown by the compounds of D1 and D2 also for the present compounds wherein the 2-substituent represents a dihydropyridine group. The alkylation of the nitrogen (R¹) is finally known from the structurally very close D3 compounds.

Therefore, the problem underlying the present application should be seen in the provision of new pyrimidone derivatives having unexpected properties over those of the closest prior art compounds (D1). In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not. In the case where comparative tests are envisaged in order to support an inventive step, these must be carried out between the compounds of the present application having the maximum structural similarity with the compounds of the closest prior art, such that the effect is shown to have its origins in the distinguishing feature of the claimed invention.

4. INDUSTRIAL APPLICABILITY

No objection.